

### REMARKS

The title of the application has been amended to be more descriptive of what is claimed. The abstract has been amended so that it contains less than 150 words. The abstract has also been amended to be more descriptive of what is claimed. The specification has been amended to include a description of Figures 4A-4D and 8A-8E in the section entitled "Brief Description of the Drawings." Support for the amendments can be found in the specification at, e.g., page 34, line 23, through page 36, line 1; page 31, lines 21-31; and page 72, line 15, through page 73, line 8. No new matter has been added by these amendments.

Claims 58-64 and 70-76 are pending in the application. In the instant Office Action, claims 58-64 and 70-76 are rejected.

Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

### THE TITLE OF THE APPLICATION

The Examiner contends that the title of the application is not descriptive and requires that Applicants provide a new title. Applicants has amended the title as required by the Examiner.

### THE OBJECTION TO THE ABSTRACT SHOULD BE WITHDRAWN

The abstract of the disclosure is objected to for exceeding 150 words. Applicants have amended the abstract such that it contains fewer than 150 words. The objection to the abstract is therefore obviated and should be withdrawn.

### THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 58-64 and 70-76 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that the phrase "deviation of one or more experimental variables from desired values lacks clear antecedent basis as to what "desired values" means. Applicants respectfully disagree with the Examiner for the reasons presented below.

Applicants respectfully submit that the Examiner's rejection is based on an erroneous interpretation of the claim language. The Examiner has misinterpreted the term "one or more experimental variables" to refer to the responses of cellular constituents. As evidence, on page 3 of the instant Office Action, the Examiner contends that "[s]uch a correct and accurate response is apparently what is meant by the 'desired value.'" The Examiner further contends that the claims are vague and indefinite because of the absence of a recitation that "'desired value' is meant to be a correct and accurate, or artifact free, biological response profile to a perturbation" (see, the instant Office Action bottom of page 3 to top of page 4). Applicants respectfully point out that, contrary to the Examiner's contention, the term "one or more experimental variables" refer to variables such as cell culture density and temperature, hybridization temperature, as well as concentrations of total RNA and/or hybridization reagents (see, e.g., specification at page 34, lines 29-32). The deviation of one or more of these variables from desired values leads to changes in cellular constituents, therefore artifacts. Such an interpretation is clear and unambiguous from the claim language. For example, claim 58 recites that each of said one or more artifacts comprises "an artifact pattern comprising measurements of changes in said cellular constituents resulting from deviation of one or more experimental variables from desired values." The claim language is clear that it is the changes in cellular constituents resulting from the deviation of the one or more experimental variables that are measured and comprised in the artifact pattern. Thus, the claim language simply does not support the Examiner's interpretation that the desired value "is meant to be a correct and accurate, or artifact free, biological response profile to a perturbation." As such, the Examiner's contention that the absence of a recitation that "'desired value' is meant to be a correct and accurate, or artifact free, biological response profile to a perturbation" in the claim language rendering the claims vague and indefinite is erroneous. Furthermore, Applicants respectfully submit that the meaning of "desired value" of experimental variables such as cell culture density, etc., is clear to one of skilled persons in the art. The rejection of claims 58-64 and 70-76 under 35 U.S.C. § 112, second paragraph, is therefore in error and should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a)  
SHOULD BE WITHDRAWN

Claims 58-61 and 71-73 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 6,232,066 ("Felder") alone, or, alternatively, over Felder in view of U.S. Patent No. 5,866,331 ("Singer"). The rejection is maintained from the Office Action dated

April 19, 2002. Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

At the outset, Applicants respectfully submit that the Examiner has misinterpreted Felder and/or Singer with respect to control measurements. As discussed in the response filed on October 18, 2002, and reiterated below, Felder teaches the use of control probes such as probes specific to genes which are not expected to be modulated by the agents being tested or which are known not to interact with the target. However, in the instant Office Action, the Examiner contends that the presently claimed invention is rendered obvious because the references teach a control experiment, e.g., an experiment in which a sample not subject to a perturbation is measured, performed side by side with the experiment in which responses to the perturbation is measured. Applicants respectfully point out that neither Felder nor Singer teach or suggest such control experiment. Indeed, Felder teaches that the control probes are "subject to the same reaction conditions as the actual experimental probes" (see, Felder col. 23, lines 41-44). Thus, Applicants respectfully submit that the Examiner's arguments rely on matter that is not present in the references, and therefore, is erroneous.

Applicants further respectfully submit that the rejection is based on an erroneous interpretation of the claim language. As discussed above, the Examiner has misinterpreted the term "one or more experimental variables" to refer to the responses of cellular constituents. Applicants has respectfully pointed out that, contrary to the Examiner's contention, the one or more experimental variables refer to variables such as cell culture density and temperature, hybridization temperature, as well as concentrations of total RNA and/or hybridization reagents (see, e.g., specification at page 34, lines 29-32). The deviation of one or more variables such as these from desired values leads to changes in values of

cellular constituents, therefore artifacts. Applicants also respectfully point out that the background levels measured without a sample in Felder, i.e., the image of the plate (see Felder, col. 33, lines 25-28), are not measurements of changes in cellular constituents.

Applicants next reiterate the arguments presented in the Amendment filed on October 18, 2002. As having been discussed in the Amendment filed on October 18, 2002, Felder teaches compositions, apparatus and methods for concurrently performing multiple biological or chemical assays. In Felder, positive control probes are used as internal standards for normalization purposes. Examples of such positive control probes include probes specific to house-keeping genes which are not expected to be modulated by, e.g., the agents being tested. Felder also teaches the use of negative control probes which are known not to interact with the target. Felder also teaches the use of probes specific to genes that are known to be induced as part of certain biological process, e.g., apoptosis, for determination of side effects of an agent. In Felder, background subtraction is also used. However, Felder's background levels are measurements of fluorescence image of the plate (see Felder, col. 33, lines 25-28). Singer teaches a method for determining the total fluorescence intensity of a single fluorochrome. In Singer, background subtraction and dark current subtraction are used.

Applicants respectfully reiterate that the presently claimed invention is directed to methods of removing artifacts from measured biological response profiles comprising measurements of a plurality of cellular constituents of a living cell or organism in response to a perturbation to said living cell or organism. The artifact patterns or artifact signatures that are removed by the presently claimed method comprise *measurements of changes or measurements of amplitudes of changes in said cellular constituents resulting from deviation of one or more experimental variables from desired values* (emphasis added). Thus, an artifact of the present invention comprises measurements of changes due to deviation of one or more experimental variables from desired values in the *same* cellular constituents for which measurements are comprised in the biological response profiles. That is, the biological response profile comprises measurements of cellular constituents, and the artifact pattern comprises measurements of changes in these same cellular constituents. This is contrary to Felder in which some "other" cellular constituents, e.g., house-keeping genes or genes relating to some side effects, are measured and used. By teaching the use of control probes specific to such other cellular constituents, Felder teaches or suggests nothing about artifacts which comprise measurements of changes in the same cellular constituents for which

measurements are comprised in the biological response profiles. As such, Felder teaches or suggests nothing about a method of removing such artifacts from measured biological response profiles.

With respect to background subtraction, Applicants respectfully point out that, as discussed above, an artifact in the presently claimed invention comprises measurements of *changes in cellular constituents resulting from deviation of one or more experimental variables from desired values*, i.e., changes in cellular constituents themselves. On the other hand, background signals are not measurements of changes in cellular constituents resulting from deviation of one or more experimental variables from desired values, but, rather, are measures of inaccuracies in signal measurements, which are independent of changes in cellular constituents. As an example, Applicants respectfully point out that, although levels of gene transcripts may be changed due to deviation of one or more experimental variables from desired values, thereby leading to artifacts in measured biological profiles, background signals arising during the determination of such changes in levels of gene transcripts are not themselves changes in levels of gene transcripts due to deviation of these experimental variables from desired values, and, therefore, are not the artifacts that are removed by the methods of the presently claimed invention. Therefore, Felder does not render the presently claimed invention obvious. Applicants respectfully submit that the rejection of claims 58-61 and 71-73 under 35 U.S.C. § 103(a) based on Felder should be withdrawn.

Singer does not teach or suggest what is missing in Felder, i.e., artifacts comprising measurements of *changes in cellular constituents resulting from deviation of one or more experimental variables from desired values*. Nor does Singer teach or suggest a method of removing such artifacts from measured biological response profiles. Therefore, Felder in view of Singer does not render the presently claimed invention obvious. Applicants respectfully submit that the rejection of claims 58-61 and 71-73 under 35 U.S.C. § 103(a) based on Felder in view of Singer should be withdrawn.

#### THE OBJECTION TO THE DISCLOSURE SHOULD BE WITHDRAWN

The disclosure is objected to for lack of description of Figures 4A-4D and 8A-8E in the section entitled "Brief Description of the Drawings." Applicants have amended the specification to include such description. The objection to the disclosure is therefore obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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## APPENDIX A